# Accepted Manuscript

Is There A Role For Pharmacokinetic/Pharmacodynamic Guided Dosing For Novel Oral Anticoagulants?

Noel Chan MD, Philip T. Sager MD, Jack Lawrence MD, Thomas's Ortel MD, PhD, Paul Reilly PhD, Scott Berkowitz MD, Dagmar Kubitza MD, John Eikelboom MD, MBBS, Jeffry Florian PhD, Norman Stockbridge MD, PhD, Martin Rose MD, Robert Temple MD, Jonathan H. Seltzer MD, MBA, MA

Please cite this article as: Chan Noel, Sager Philip T., Lawrence Jack, Ortel Thomas's, Reilly Paul, Berkowitz Scott, Kubitza Dagmar, Eikelboom John, Florian Jeffry, Stockbridge Norman, Rose Martin, Temple Robert, Seltzer Jonathan H., Is There A Role For Pharmacokinetic/Pharmacodynamic Guided Dosing For Novel Oral Anticoagulants?, *American Heart Journal* (2017), doi: 10.1016/j.ahj.2017.10.002

**Is There A Role For Pharmacokinetic/Pharmacodynamic Guided Dosing For Novel Oral Anticoagulants?**

Abstract:

Article: 4333 words

Tables: 2

Figures : 2

**Authors:**

| | |
|---|---|
| **Noel Chan, MD** | **McMaster University, Ontario, Canada** |
| **Philip T. Sager, MD** | **Stanford University, Palo Alto, CA** |
| **Jack Lawrence, MD** | **Bristol Myers Squibb, Princeton NJ** |
| **Thomas's Ortel, MD, PhD** | **Duke University, Durham, North Carolina** |
| **Paul Reilly, PhD** | **Boehringer Ingleheim, Ridgefield, CT** |
| **Scott Berkowitz, MD** | **Bayer, Parsippany, NJ** |
| **Dagmar Kubitza, MD** | **Bayer AG, Wuppertal, Germany** |
| **John Eikelboom, MD, MBBS** | **McMaster University, Ontario, Canada** |
| **Jeffry Florian, PhD** | **Food and Drug Administration, Silver Spring, MD** |
| **Norman Stockbridge MD, PhD** | **Food and Drug Administration, Silver Spring, MD** |
| **Martin Rose, MD** | **Food and Drug Administration, Silver Spring, MD** |
| **Robert Temple, MD** | **Food and Drug Administration, Silver Spring, MD** |
| **Jonathan H. Seltzer, MD, MBA, MA** | **ACI Clinical, Bala Cynwyd, PA** |

**Corresponding Author: Noel Chan, MD**

Email:  Noel.Chan@monashhealth.org

**Affiliations:** Thrombosis & Atherosclerosis Research Institute (TaARI)

C5-116 DBCVRI

237 Barton Street East

Hamilton, Ontario

L8L 2X2

Canada

Ph:      905-521-2100 Ext 40727

Fax:     905-575-2646

**Abstract**

The novel direct oral anticoagulants (NOACs) represent a major advance in oral anticoagulant therapy, and are replacing vitamin K antagonists as the preferred options for many indications. Given in fixed doses without routine laboratory monitoring, they have been shown to be at least as effective in reducing thromboembolic stroke as dose-adjusted warfarin in phase 3 randomized trials and less likely to cause hemorrhagic stroke.

Pharmacokinetic and/or pharmacodynamic sub-analyses of the major NOAC trials in patients with atrial fibrillation (AF) have established relationships between clinical characteristics, and drug levels and/or pharmacodynamic responses with both efficacy and safety. Based on these analyses, pharmaceutical manufacturers and regulatory authorities have provided contraindications and dosing recommendations based on clinical characteristics that are associated with drug levels and/or pharmacodynamic responses, stroke reduction, and bleeding risk to optimize the risk-benefit profile of the NOACs in the real world. The current fixed dosing strategy of NOACs have triggered discussions about the potential value of laboratory monitoring and dose adjustment in customizing drug exposure to further improve the safety and efficacy of the NOACs in patients with AF.

As there is neither high quality evidence nor consensus about the potential role of laboratory monitoring and dose adjustment for the NOACs, a Cardiac Research Safety Consortium "think tank" meeting was held at the American College of Cardiology Heart House in December 2015 to discussions these issues.  This manuscript reports on the deliberations and the conclusions reached at that meeting

**Introduction**

The novel direct oral anticoagulants (NOACs) represent a major advance in oral anticoagulant therapy, and are replacing vitamin K antagonists (such as warfarin) as the preferred options for many indications (1). Four NOACs are now licensed for stroke prevention in atrial fibrillation (SPAF) in several jurisdictions: dabigatran, which inhibits thrombin; and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa (FXa) (2-5). Given in fixed doses without routine laboratory monitoring, all four were shown to be at least as effective in reducing thromboembolic stroke as dose-adjusted warfarin in phase 3 randomized trials and less likely to cause hemorrhagic stroke (2-5). These results have been subsequently supported in several post-marketing studies (1). Because of their ease of use and favorable risk-benefit profile, the NOACs have the potential to reduce the global burden of thrombosis and make long term anticoagulation safer.

Pharmacokinetic and/or pharmacodynamic (PK/PD) sub-analyses of the major NOAC trials in SPAF have established relationships between clinical characteristics, and drug levels and/or pharmacodynamics responses with both efficacy and safety (6-9). Based on these analyses, pharmaceutical manufacturers and regulatory authorities have provided contraindications and dosing recommendations based on clinical characteristics that are associated with drug levels and/or pharmacodynamic responses, stroke reduction, and bleeding risk to optimize the risk-benefit profile of the NOACs in the real world. With fixed dosing of NOACs, some patients have drug levels that may be considered too high or too

low, which may increase their risk of bleeding or thromboembolism, respectively. These observations have challenged the current fixed dosing strategy of NOACs and have triggered discussions about the potential value of laboratory monitoring and dose adjustment in customizing drug exposure to further improve the safety and efficacy of the NOACs in patients with AF.

As there is neither high quality evidence nor consensus about the role of laboratory monitoring and dose adjustment for the NOACs, a Food and Drug Administration (FDA)/Cardiac Safety Research Consortium (CSRC) sponsored Think Tank was convened at the Heart House in December 2015. The aim of the Think Tank was to bring together experts and various stakeholders to discuss the potential role of PK/PD-guided dosing for the NOACs and to highlight key issues from clinical, academic, industry, and regulatory perspectives. This white paper summarizes the discussion about this important issue. In this manuscript, we 1) briefly summarize the rationale and evidence for fixed doses of the NOACs in patients with atrial fibrillation, 2) describe perceived limitations of current dosing strategies, 3) discuss the rationale, potential role and challenges of laboratory monitoring of NOACs and highlight the gaps in evidence, 4) bring perspective to the issue of inter-patient drug level variability in the setting of the challenges faced with NOACs implementation in the real world; and 5) provide consensus recommendations.

**From INR-guided warfarin dosing to NOAC dosing without laboratory monitoring:**

For over 60 years, vitamin K antagonists (VKA), such as warfarin, were the only orally administered anticoagulant for thromboembolism prevention and treatment. Although effective, two pharmacological considerations prevent the safe use of warfarin in a fixed dose regimen, and consequently, limit its use. First, the dose-response relationship for the anticoagulant effect of warfarin is unpredictable; fixed doses of warfarin result in marked inter- and intra-patient variability in its anticoagulant effect. The wide inter-patient variability occurs because of multiple drug and food interactions, and pharmacogenetic differences. Second, warfarin is limited by a narrow therapeutic range and the difficult task of maintaining

4

the anticoagulant effect within the therapeutic range even with frequent INR monitoring (10-13).

With marked variability in its anticoagulant effect, and strong relation between anticoagulant effect and thrombosis or bleeding risk, adjusting the dose of warfarin according to the international normalized ratio (INR), a standardized measure of its anticoagulant effect, has become an essential component for dosing vitamin K antagonists such as warfarin. The goal is to maintain the anticoagulant intensity within an appropriate therapeutic range (typically an INR range of between 2.0 to 3.0 for SPAF), a universally accepted practice supported by several randomized trials over the last several decades (14). Maintaining the INR in the target range, however, is challenging for clinicians in the real world and inconvenient for patients. Despite an INR-guided dosing strategy, many patients receiving warfarin are often outside of the established target range (mean time in therapeutic range in US ~ 55%) and the incidence of clinically significant bleeding events is substantial (15). Importantly, because of the inconveniences imposed by laboratory monitoring and dosing, and the fear of bleeding, warfarin is systemically underutilized in eligible patients, adding to the global burden of thrombosis (16, 17).

These limitations prompted the development of oral anticoagulants with better pharmacological profiles: dabigatran, rivaroxaban, apixaban, and edoxaban. Unlike warfarin, the relatively predictable dose-exposure (PK), and dose-response (PD) relationships in early clinical trials supported the concept that fixed doses, without the need for laboratory monitoring, could be used to achieve appropriate exposure for most patients, and paved the way for the phase 3 trials comparing fixed doses of NOACs with INR-guided dosing of warfarin (2-5).

**NOACs in atrial fibrillation**

*Dose-response relationship*

In the pivotal SPAF trials, the four NOACs were compared with INR-adjusted dose warfarin in 71 683 patients with non-valvular AF (18). The NOAC dosing regimens varied according to dose ranges, dosing frequency (once daily vs. twice daily), and post-randomization dose adjustment made at baseline or during the trials (Table 1). In RE-LY and ENGAGE-AF trials, investigators compared two doses of dabigatran etexilate (110 and 150 mg BID) and edoxaban (30 and 60 mg daily) with warfarin, respectively, whereas in ROCKET-AF (rivaroxaban 20 mg daily) and ARISTOTLE (apixaban 5 mg BID), one NOAC dose was compared to warfarin (2-5). The latter two trials, however, incorporated a post-randomization clinical dose reduction strategy based on the presence of certain baseline clinical characteristics associated with increased drug exposure and bleeding risk (Table 1). In addition to the randomized comparison of two edoxaban doses, the ENGAGE-AF trial also incorporated a post-randomization dose reduction strategy based on baseline patient characteristics or concomitant use of P-glycoprotein (P-gp) inhibitors during the trial.

Although the NOACs differ in their pharmacokinetic properties, and in their pharmacological targets (thrombin and FXa), fixed doses of all four NOACs were at least as effective in reducing stroke and systemic embolism as dose-adjusted and monitored warfarin and were associated with less hemorrhagic stroke in the pivotal phase 3 trials. Two observations are worth summarizing concerning NOACs dosing and clinical outcomes. First, in comparison to INR modified doses warfarin, the NOACs exhibited a consistent and predictable relation between dose and clinical outcomes. In the two trials comparing high and low doses of NOACs with warfarin, the higher NOAC dose was typically associated with superior reduction in ischemic stroke whereas the lower NOAC dose was associated with less major bleeding. For instance, in the RE-LY trial, dabigatran 150 mg BID reduced the risk of ischemic stroke by 24% (risk reduction [RR] 0.76; 95% confidence interval [CI]: 0.60 – 0.98) and caused a similar risk of major bleeding when compared to warfarin (RR 0.93; 95% CI: 0.81 – 1.07) whereas dabigatran 110 mg BID was associated with less favorable risk reduction in ischemic stroke (RR 1.11; 95% CI: 0.89 – 1.40) and less major bleeding (RR

0.80; 95% CI 0.69 – 0.93) (2). In the ENGAGE AF trial, edoxaban 60 mg daily was at least as effective as warfarin in reducing the risk of ischemic stroke (RR 1.00; 95% CI: 0.83 – 1.19) and was associated with reduced risk of major bleeding when compared to warfarin (RR 0.80; 95% CI: 0.71 – 0.91) whereas edoxaban 30 mg daily was associated with more ischemic stroke than warfarin (RR 1.41; 95% CI: 1.19 -1.67) and less major bleeding (RR 0.47; 95% CI 0.41 – 0.55)(5).

Second, in a meta-analysis, NOACs produced about a 10% reduction in mortality irrespective of dose (RR 0.90; 95% CI: 0.85 – 0.95) when compared to warfarin (18), suggesting that although the lower doses are less effective at reducing ischemic stroke than the higher doses, this reduced efficacy is counterbalanced by less bleeding with lower dose NOACs. For example, although the lower dose edoxaban was associated with a significant increase in ischemic stroke, this dose was associated with a significant reduction in mortality (RR 0.87; 95% CI; 0.79 – 0.96). This finding is relevant because it suggests that the range of NOAC doses currently used is close to the "sweet spot" for net benefit.

*Patient characteristics- and NOAC concentration-response relationships*

When administered in fixed doses in patients with AF, each NOAC results in a range of levels (PK) and anticoagulant effects (PD). Sub-analyses of the pivotal trials have shown that both clinical and PK-PD covariates are predictors of clinical outcome and have clarified the relationships between these covariates and clinical response in NOAC-treated patients (Figure 1) (6-9). First, patient characteristics influence clinical outcome apart from their effect on NOAC exposure, highlighting the complex interplay between the clinical and the PK-PD covariates. Both the RE-LY and ENGAGE-AF sub-studies suggest that the association between NOACs concentration and clinical outcome is heavily modulated by clinical characteristics of patients, especially at the extremes of the drug concentrations (6, 7). As shown in the RE-LY sub-study, age is an important covariate (Figure 2) (6). Increased age is a risk factor for stroke and bleeding but it also increases dabigatran concentrations. Therefore, for a given concentration of dabigatran, the rates of ischemic stroke, major

bleeding, and their trade-off will vary according to age. Second, concentration-response relationships for extracranial major bleeding, intracranial bleeding and stroke are unique for each outcome. For major bleeding, increasing NOAC exposure results in steady increase in the risk of bleeding, whereas event rates for stroke decline less steeply after a threshold (e.g. approx. 100 ng/ml for edoxiban -- see Figure 2) appears to plateau with higher NOAC exposure. The risk of stroke, however, increases sharply below a critically low NOAC exposure (e.g. 50 ng/ml). In contrast to warfarin, the risk for intracranial bleeding is low for NOACs, and is not substantially affected by increasing exposure (2-5, 7).

It should be noted that there are some considerations and data limitations regarding the NOAC exposure-response curves. First, exposures for patients were determined by limited sampling at 1-2 occasions. In addition, drug concentrations were not measured at the time of acute stroke or bleeding events.

**Improving risk-benefit: rationale for NOAC dose-adjustment**

While fixed dosing of NOACs produces favorable results, the PK-PD findings raise the possibility that the risk-benefit of NOACs could be improved for individual patients. Although no formally validated therapeutic ranges exist, some patients have NOAC levels that are considered too high or too low, which are associated with bleeding or thromboembolism, respectively. For example, while dabigatran 150mg BID consistently produced trough levels above 50 ng/ml, some patients had markedly high levels, which predisposed them to the risk of bleeding (Figure 2) (6). Conversely, with the 110mg dose, most patients had trough levels below 200 ng/mL, associated with lesser rates of bleeding, but some had levels below 50 ng/mL, predisposing to higher risk of thromboembolism. If these patients could be reliably identified by either clinical factors or PK-PD measurements, adjusting the NOAC dose could bring the drug level into a more desirable or circumscribed range, thereby mitigating the risk associated with 'extreme' drug levels. Because the relationship between drug level and major bleeding is steeper than with stroke, and has no clear threshold based on available

8

data, proponents argue that dose adjustment strategies aimed at reducing drug level in patients with NOAC overexposure may reduce the risk of bleeding without substantial loss in efficacy. Targeting patients with NOAC underexposure or whose characteristics predispose to underexposure is also possible but distinguishing patients with true underexposure from those whose levels are low due to poor adherence would still remain a challenge. As summarized in Figure 1, there are two possible ways of tailoring NOAC dose, based on either clinical factors or PK-PD parameters.

*Dose adjustment based on clinical factors*

Various clinical factors (e.g., renal function, age, use of P-gp/CYP450 inducers or inhibitors, and weight) influence NOAC exposure. Knowledge of the effect of these factors on blood levels could be used to ensure that drug exposure falls in a circumscribed range for almost all patients, without the need for NOAC level monitoring, provided enough dosing strengths were available. With a dose adjustment strategy based on clinical factors, the dose of NOAC is tailored based on the presence of specific clinical characteristics (such as renal function, age, weight, previous history of stroke and concomitant medications) that correlate with drug level and/or clinical outcome such as bleeding or stroke. Dose adjustment for these characteristics was implemented in ROCKET-AF, ARISTOTLE, and the ENGAGE-AF trials to prevent NOAC over-exposure and bleeding in at-risk patients (3-5). Subsequently, in drug labeling, the pharmaceutical manufacturers and regulators have provided clinicians with dosing recommendations and modifications based on patient characteristics such as advanced age, reduced renal function, low body weight, and concomitant administration of potent P-gp inhibitors; factors associated with increased drug exposure and increased bleeding risk. Compared to PK-PD guided dose adjustment, the practice of dose adjustment based on clinical factors is well supported, is routinely utilized in labeling for most therapeutics, and can be readily and widely implemented. Thus, a *post-hoc* analysis of the RE-LY study reported that the efficacy and safety of dabigatran was further improved if dose was allocated based on clinical characteristics according to the European guideline

9

recommendations (19). Moreover, the post-randomization clinical dose adjustment strategies employed in the trials showed that bleeding was reduced compared to warfarin without appreciable loss in efficacy (Table 2) (7, 20, 21). The ENGAGE-AF study, one of the largest trials adopting a post-randomization clinical dose adjustment strategy, over a four-fold dose range, proved that reducing edoxaban dose based on the presence of at-risk clinical factors successfully prevented edoxaban overexposure, which in turn led to additional reduction in bleeding. For instance, in those patients allocated to the higher dose arm (edoxaban 60 mg), there was no difference in the treatment effect on ischemic stroke between those with or without dose reduction (ischemic stroke: p-interaction = 0.91) but the dose reduction based on clinical characteristics (presence of creatinine clearance between 30 to 50 ml/min or weight ≤ 60 kg, or concomitant use of verapamil or quinidine) provided an improvement in safety (major bleeding: p-interaction=0.02) (7).

*PK-PD guided dose adjustment*

A PK-PD guided approach, in contrast to a fixed dose of NOACs that produces variable exposure in a population, might possibly provide a more accurate representation of NOAC exposure than clinical characteristics. Therefore, by monitoring drug concentrations, it is hypothesized that 1) there is a desirable range of concentrations (sweet spot) for efficacy and safety, 2) the test will accurately and reliably identify patients outside this "sweet spot"; and 3) like INR-guided warfarin dosing, if outliers could be identified, modifying NOAC dose would shift levels to a "sweet spot", resulting in reduced bleeding and thromboembolism. Unlike dose adjustment based on clinical factors, PK-PD guided strategy is potentially complex (drugs with short terminal half-lives require precise timing for sampling and interpretation), adds to cost; and high quality evidence supporting the clinical benefit of this strategy is presently lacking. However,  Figure 2  suggests  strategy based trough values which would be more straightforward.  In addition, the sweet spot may be different for patients with different degrees of bleeding or thromboembolism risk, however this doesn't seem to be the case for patient age or renal function.   A PK-PD guided strategy would likely

need to be confirmed by additional investigations (see below) and the relative paucity of available PK sampling in the previous studies would add challenges to the development of such an approach. Although rational in principle, because of the lack of high quality evidence, the concept for PK-PD guided NOAC dosing requires further scientific investigations if it is to be pursued. Even if proven, several challenges will need to be addressed for effective implementation of a NOAC dose adjustment strategy based on the results of drug level testing.

**PK-PD guided dose adjustment strategy: uncertainties and challenges**

In practice, a PK-PD guided strategy involves several intertwined steps, each presenting its own challenges and uncertainties. Key considerations include 1) measurement of drug level, 2) interpretation of level based on an established therapeutic range, 3) dose adjustment to achieve the desirable range; and 4) frequency of re-testing.

*Measuring NOAC levels*

NOAC drug level need to be reliably and accurately measured with reasonable turnaround time. Routinely available clotting assays (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) are not suitable for PK-PD guided dosing because they lack analytical sensitivity and specificity to accurately quantitate a specific NOAC's levels or its anticoagulant effect. Although liquid chromatography tandem mass spectrometry (LC-MS/MS) and calibrated clotting or chromogenic assays can accurately and reliably quantitate NOAC levels, they are not readily available in clinical practice. Calibrated clotting or chromogenic assays, which show good agreement with LC-MS/MS, can theoretically be implemented in the clinical laboratory as they are more compatible with existing diagnostic platforms. Quantitative assays for dabigatran include the dilute thrombin time (e.g., Hemoclot®), and ecarin chromogenic assay, while for the direct factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, quantitative assays are based on modified chromogenic anti-FXa assay (22, 23).

11

The current challenges with these quantitative assays are: a) assays are not widely available (e.g., in the US, assays for this intended purpose are not yet licensed), and b) international standardization in methods is lacking. Because diagnostic tests have a regulatory pathway depending upon intended use, more stringent licensing requirements may impede the implementation of such assays, unless pragmatic solutions are proposed. Even if these assays are licensed, inter-laboratory variability in measurements may lead to differences in drug level reporting, highlighting the need of standardization to ensure accurate and reproducible results on which to base dose adjustments.

*Identifying patients with 'extreme' levels*

In addition to reliable and accurate assays, optimal sampling time, established therapeutic ranges or cut-offs, and the number of measurements are critical factors in correctly identifying patients with 'extreme' levels in whom dosing adjustment might be required. A challenge in interpreting a single measurement is that some 'extreme' levels are due to inaccurate reporting of dosing times, missed doses or double doses taken inadvertently. The optimal time and frequency of sampling (trough, peak, or both) is unclear. If a sampling time is chosen, the level at this sampling time should ideally exhibit good correlation with NOAC exposure and clinical outcome. Trough levels appear to satisfy these two attributes (6,7). To correctly classify patients as needing a dose adjustment, it is important to establish a desirable range of drug levels. This ideal range varies according to the outcome to be optimized (bleeding, stroke, or both), and may also depend on patient group (elderly, renally impaired, and high bleeding risk). Finally, because identification of outliers is susceptible to regression to the mean, one single measurement may not reliably identify patients with extreme levels, especially in the case of drugs with substantial within-subject variability in plasma concentrations, such as dabigatran (24).

*Dose adjustments to achieve desirable levels and frequency of re-testing*

Faced with a patient with extreme NOAC levels, the precise dose-adjustment needed to achieve the desirable range, and the frequency of repeat dose adjustments have not been

12

established. Because limited dose strength of NOAC are licensed, dose adjustment is restricted to these dose strengths, highlighting the need for additional dose strengths. More data are needed on the stability of drug level after dose-adjustment and on within-patient variability in patients with the more extreme NOAC levels to inform on frequency of re-testing and dose-adjustment.

**Other relevant considerations**

*What type of evidence would be acceptable?* Although a clinical outcome-based randomized controlled trial of fixed versus adjusted dose NOAC would be most desirable if this approach was to be pursued and offer the highest quality evidence that could change practice, such a trial would require a large number of patients, take years to complete, and would be very costly. Surrogate-based designs (either observational or randomized) may offer a pragmatic approach to inform on several aspects of PK-PD monitoring and dose adjustment.

*Which clinical outcome to optimize?* Opinions were divided as to which clinical outcome can be optimized with a PK-PD guided approach. Participants agreed that ischemic stroke confers greater morbidity and mortality than major bleeding, excluding an intracerebral bleed. A closer look at the NOAC trials, however, offers the following observations: 1) absolute rates of stroke are lower (1-2% per year) compared to the rates of major bleeding (~3% per year), 2) dosing with high-dose NOACs (the default in clinical practice) result in only a small proportion of patients with a low drug level, except in the case of edoxaban in patients with excellent renal function, 3) it is difficult to differentiate true NOAC underexposure from lack of adherence with trough drug level; and 4) the differential slope of the bleeding and ischemic stroke curve suggests that lowering NOAC exposure in patients with high levels is likely to reduce bleeding. These considerations suggest that bleeding, resulting from very high NOAC levels, may be the most feasible outcome to optimize with a PK-PD guided approach; however, lowering NOAC dosing too much might be expected to compromise efficacy.

13

*Which population to target?* An unselected or a selected population could be considered for the testing levels and dose adjustment. When dosed according to their labels, most patients receiving NOACs will have desirable levels and favorable outcomes compared with warfarin, implying that testing an unselected population may be inefficient, costly, and provide at best marginal benefit. Selecting patients based on clinical characteristics predisposing to extreme levels or increased risk of bleeding or stroke has the advantage of ensuring that this intervention is appropriately targeted to patients who would benefit the most.

*What are the challenges of implementation?* Despite the relative simplicity of clinical dose adjustment, and wide availability of dosing criteria, many patients are under-dosed as exemplified by an overuse of low dose NOACs in the community (25, 26). PK-PD guided dosing, a more complex approach, is therefore at even higher risk of implementation failure. There are several prerequisites for effective implementation of a PK-PD guided approach: 1) accurate identification of patients with extreme levels, 2) appropriate clinical interpretation, and 3) an effective action plan. To ensure successful implementation, appropriate physician education, clear parameters for utilization, and specific instructions via dosing algorithm are required.

**PK-PD guided dose adjustment in perspective**

Post-marketing studies of NOACs have confirmed their safety and efficacy but have also identified problems. The major problems facing anticoagulant therapy, including the NOACs ,are: underutilization, under-dosing, and non-adherence (factors contributing to the burden of thrombosis) (1). Observational studies show that there continues to be a proportion of AF (up to 50%) who are not receiving anticoagulant therapy (17). Due to bleeding risk aversion, some physicians are either unwilling to prescribe the NOACs or prescribe low-dose NOACs contrary to the NOAC label despite knowledge that dose selection is critical for achieving maximum benefit (25, 26). Viewed in this light, these problems are greater in magnitude and scope, resulting in a substantial number of preventable thromboembolic events, than the

14

putative problem related to inter-patient variability in NOAC exposure. If a PK-PD approach is adopted, it might help refine dosing and help prevent bleeding but the impact on NOAC uptake and compliance is difficult to predict and may not be contributory to a meaningful extent. On the other hand, dose adjustment for such factors as renal function, age, and concomitant therapy may not be as disruptive.

**Concluding comments**

Several conclusions and consensus positions were reached during this meeting. First, the panel agrees that the overwhelming problems facing NOACs are their underutilization, under dosing and non-adherence, and advocate that efforts should focus on optimizing NOACs utilization, proper patient selection and dosing; and maximizing adherence. Second, the panel acknowledges that proper dose selection is critical for achieving the maximum benefit of the NOACs. Evidence from trials support dose adjustment based on clinical factors predisposing to overexposure or risk of bleeding (eg., age, renal function, concomitant medications, and bleeding risk). Routine PK-PD measurements to guide NOAC dosing cannot currently be recommended due to the lack of reliable tests, lack of clinical evidence of benefit, and data to guide appropriate dosing. If there were a reliable licensed test, it may be useful for measuring NOAC levels or PD effects to guide decisions in selected clinical situations (e.g., major bleeding, urgent surgery or invasive procedures, thrombolysis for acute stroke, recurrent thromboembolic events; and NOAC overdose) and possibly in selected patients (with relevant clinical characteristics such as advanced age, low body weight, renal impairment, on hemodialysis, or on multiple concomitant medications). Third, the panel recognizes the potential of using a PK-PD guided dosing to improve the risk-benefit trade-off of NOACs in selected patients and believes that this approach is worthy of further scientific investigations as there are significant unknowns. As clinical outcome based randomized trials to specifically study this aspect would be challenging, the first step in the evaluation of this approach may be to consider using other pragmatic options.

**References:**

15

1.      Chan NC, Eikelboom JW, Weitz JI. Evolving Treatments for Arterial and Venous Thrombosis. Role of the Direct Oral Anticoagulants. Circ Res 2016;118(9):1409-24.

2.      Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2009;361(12):1139-51.

3.      Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. New England Journal of Medicine. 2011;365(10):883-91.

4.      Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2011;365(11):981-92.

5.      Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2013;369(22):2093-104.

6.      Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, et al. The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients. The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). Journal of the American College of Cardiology. 2014;63(4):321-8.

7.      Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. The Lancet. 2015;385(9984):2288-95.

8.      Food and Drug Administration. Rivaroxaban Medical Review 2011 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000MedR.pdf.

9.      Food and Drug Administration. Apixaban Medical Review 2012 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf.

10.     Hylek EM, Singer DE. RIsk factors for intracranial hemorrhage in outpatients taking warfarin. Annals of Internal Medicine. 1994;120(11):897-902.

11.     Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. New England Journal of Medicine. 2003;349(11):1019-26.

12.     Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briet E. Optimal Oral Anticoagulant Therapy in Patients with Mechanical Heart Valves. New England Journal of Medicine. 1995;333(1):11-7.

13.     Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1(2):84-91.

14.     Hirsh J. Solving the mystery of excessive warfarin-induced bleeding: A personal historical perspective. Thrombosis and Haemostasis. 2014;112(5):853-6.

15.     Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. Journal of Managed Care Pharmacy : JMCP. 2009;15(3):244-52.

16.     Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review. The American Journal of Medicine. 2010;123(7):638-45.e4.

17.     Hsu JC, Maddox TM, Kennedy KF, et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: Insights from the NCDR PINNACLE registry. JAMA Cardiology. 2016;1(1):55-62.

18.     Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014;383(9921):955-62.

19.     Lip GYH, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S. Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. Thrombosis and Haemostasis. 2014;111(5):933-42.

20.     Fox KAA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. European Heart Journal. 2011;32(19):2387-94.

21.     Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. European Heart Journal. 2014;35(28):1864-72.

22.     Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory Measurement of the Anticoagulant Activity of the Non–Vitamin K Oral Anticoagulants. Journal of the American College of Cardiology. 2014;64(11):1128-39.

23.     Dale BJ, Chan NC, Eikelboom JW. Laboratory measurement of the direct oral anticoagulants. British journal of haematology. 2016;172(3):315-36.

24.     Chan NC, Coppens M, Hirsh J, Ginsberg JS, Weitz JI, Vanassche T, et al. Real-world variability in dabigatran levels in patients with atrial fibrillation. Journal of Thrombosis and Haemostasis. 2015;13(3):353-9.

25.     Nguyen E, White CM, Patel MR, Fields LE, Peacock WF, Crivera C, et al. Doses of apixaban and rivaroxaban prescribed in real-world United States cardiology practices compared to registration trials. Current Medical Research and Opinion. 2016;32(7):1277-9.

26.     Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. Journal of the American College of Cardiology. 2016;68(24):2597-604.

**Table 1**: Dosing of NOACs in SPAF trials and post-licensing

| | Dabigatran[2] | Rivaroxaban[3] | Apixaban[4] | Edoxaban[5] |
|---|---|---|---|---|
| Mode of Action | Direct thrombin inhibitor | FXa inhibitor | FXa inhibitor | FXa inhibitor |
| Phase III clinical trial | RE-LY | ROCKET-AF | ARISTOTLE AVERROES | ENGAGE-AF |
| Dose in trials and criteria for post-randomization dose adjustment | 150 mg BID 110 mg BID* (No post-randomization dose adjustment) | 20 mg QD 15 mg QD if: CrCl=15-50 ml/min | 5 mg BID 2.5 mg BID if: at least 2 of Age ≥ 80 yrs Weight ≤ 60 kg Creatinine ≥ 1.5 mg/dL | 60 mg QD 30 mg QD 15 mg QD Reduced dose if: CrCl = 30-50 ml/min Weight ≤ 60 kg Concomitant use of verapamil or quinidine |
| FDA dosing recommendations<br><br>Standard dose and criteria for reduced dose | 150 mg BID<br><br>75 mg BID if: CrCl=15-30 ml/min | 20 mg QD<br><br>15 mg QD if: CrCl=15-50 ml/min | 5mg BID<br><br>2.5 mg BID if: at least 2 of Age ≥ 80 yrs Weight ≤ 60 kg Creatinine ≥ 1.5 mg/dL | 60 mg QD<br><br>30 mg QD if: CrCl 15 – 50 ml/min 60 mg QD if CrCl >50-95 ml/min Do not use if: CrCl >95 ml/min |

*not approved by FDA
References (2-5)

**Table 2**: Effect of post-randomization dose adjustment (according to clinical criteria) in the major trials evaluating NOACs for stroke prevention in atrial fibrillation

| Outcome | Trial/ NOAC | Rates in reduced dose NOAC %/yr | Rates in warfarin control %/yr | HR 95% CI | Rates in standard dose NOACs %/yr | Rates in warfarin control %/yr | HR 95% CI | P-int |
|---|---|---|---|---|---|---|---|---|
| Stroke/SEE | ROCKETAF[20] | 2.95 | 3.44 | 0.86 (0.63-1.17) | 1.92 | 2.16 | 0.89 (0.73-1.08) | 0.85 |
| Major bleeding | Rivaroxaban | 4.49 | 4.70 | 0.95 (0.72-1.26) | 3.39 | 3.17 | 1.07 (0.91-1.26) | 0.48 |
| Stroke/SEE | ARISTOTLE[21] | 1.65 | 3.13 | 0.52 (0.25-1.08) | 1.54 | 2.05 | 0.75 (0.55-1.03) | 0.52 |
| Major bleeding | Apixaban | 3.29 | 6.54 | 0.55 (0.31-0.94) | 3.21 | 5.00 | 0.66 (0.53-0.83) | 0.48 |
| Stroke/SEE | ENGAGE-AF[7] | 1.79 | 2.21 | 0.81 (0.58-1.13) | 1.00 | 1.29 | 0.78 (0.61-0.99) | 0.85 |
| Major bleeding | High-dose edoxaban | 3.05 | 4.85 | 0.63 (0.50-0.81) | 2.66 | 3.02 | 0.88 (0.76-1.03) | 0.023* |
| Stroke/SEE | ENGAGE-AF[7] | 2.36 | 2.21 | 1.07 (0.79-1.46) | 1.38 | 1.29 | 1.07 (0.86-1.34) | 0.99 |
| Major bleeding | Low-dose edoxaban | 1.50 | 4.85 | 0.31 (0.23-0.42) | 1.65 | 3.02 | 0.55 (0.46-0.65) | 0.002* |

HR: hazard ratio; P-int: P-interaction; SEE: systemic embolism; yr: year
* significant interaction

Note: Table 2 examines the impact of post-randomization dose reduction (based on clinical criteria) on efficacy and safety in ROCKET-AF, ARISTOTLE, and ENGAGE-AF trials. These trials differ in the baseline risk of enrolled population. In general, the treatment effect of the NOACs on stroke/SEE reduction is similar in the reduced dose and standard dose arms. For the ENGAGE-AF trial, post-randomization dose reduction provided even greater safety compared with warfarin (major bleeding: higher dose p-interaction 0·02, lower dose p-interaction=0·002) while preserving the efficacy of edoxaban (stroke or systemic embolic event: higher dose p-interaction=0·85, lower dose p-interaction=0·99). Data obtained from references (7,20,21). Note that different types of strokes are affected by higher doses. For instance high dose edoxaban and dibigitran had favorable effect on thromboembolic stroke; whereas data do support hemorrhagic stroke benefit of higher doses
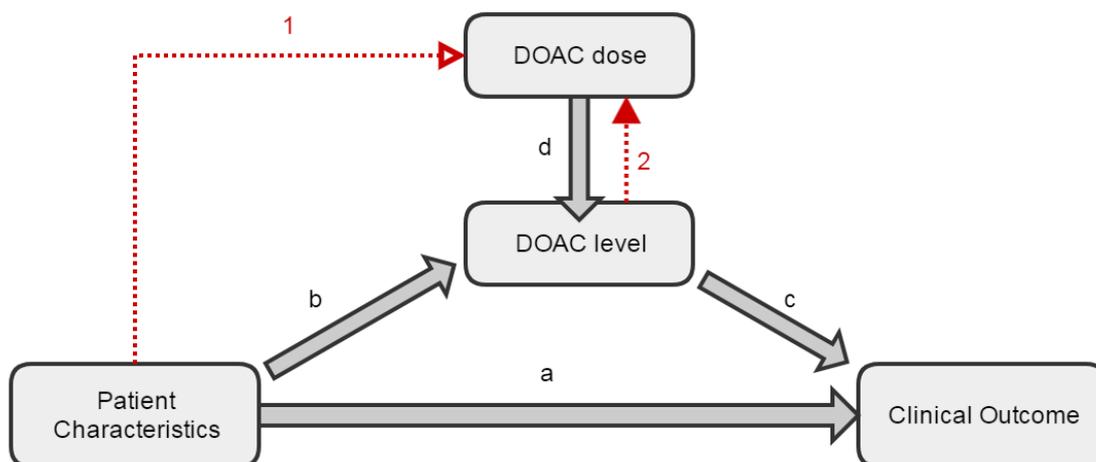
**Figure 1**: Suggested relationships among patient characteristics, NOAC level and clinical outcome

**Caption**: Age and renal function are two patient characteristics which influence clinical outcome directly (arrow a) or indirectly via their effect on NOAC level (arrows b,c).Patient characteristics modulate exposure to NOAC, and the effect of NOAC exposure on clinical outcome. For example, increasing age predisposes to increased exposure; the two effects act in synergy to increase bleeding. Two possible ways of modifying NOAC level or exposure by adjusting dose are: dotted arrow 1) adjusting dose according to clinical characteristics of patients: this is the approach taken in ROCKET-AF, ARISTOTLE, AVERROES, and ENGAGE-AF, and in the post-licensing of dabigatran etexilate; and dotted arrow 2) adjusting dose based on PK sampling.
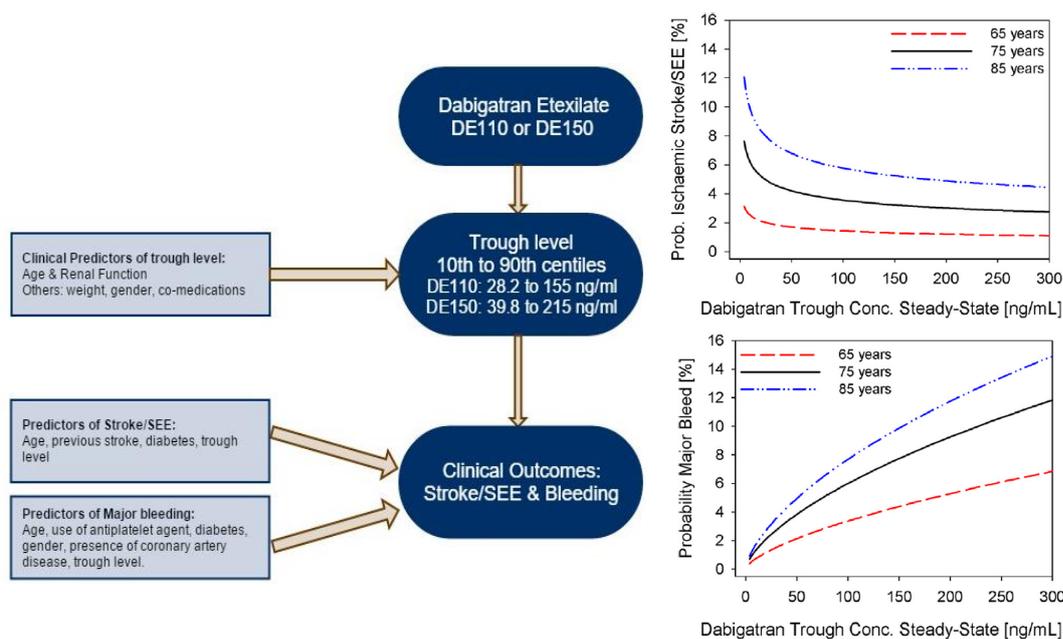
**Figure 2**: Factors contributing to variability in dabigatran pharmacokinetics and clinical outcomes

**Caption**: There is a complex interplay between the clinical characteristics and dabigatran level such that any effect that dabigatran concentration has on clinical outcome is confounded by clinical characteristics of patients. The right inset illustrates the impact of age and concentration on stroke and bleeding risk. The combination of high dabigatran level and older patients resulted in substantial increase in bleeding when compared to younger patients with the same concentrations. Similarly, at the low level, while there is an increase in the risk of stroke below a critical dabigatran level, the risk increase is magnified by increasing age. Data obtained from reference (6).